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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,360	03/04/2002	Petros Tsipouras	IK-110.3(C)	1541
47670 7590 09/11/2007 KELLEY DRYE & WARREN LLP 400 ATLANTIC STREET, 13TH FLOOR STAMFORD, CT 06901			EXAMINER CLOW, LORI A	
			ART UNIT 1631	PAPER NUMBER
			MAIL DATE 09/11/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/091,360	TSIPOURAS ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16, 18, 40, 41, 45 and 47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16, 18, 40, 41, 45, and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicants' response, filed 5 July 2007, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 16, 18, 40, 41, 45, and 47 are currently pending. Claims 1-15, 17, 19-39, 42-44, and 46 have been cancelled.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 16, 18, 40, 41, 45, and 47 are drawn to a computer-controlled method for automated rare cell identification comprising the programmed steps of instruction of starting a microscope objective, measuring a pre-set criteria, and identifying a detected cell.

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In this case, programmed steps constitute nonfunctional descriptive material, as no requisite functionality is present to satisfy the practical application requirement. Merely claiming nonfunctional descriptive material, i.e. abstract ideas, stored in a computer-readable medium, in a computer, does not make the claims statutory. Further, data structures, as in a "program" are descriptive material, *per se* and are not statutory because they are not capable of causing a functional change in the computer. See, e.g., Warmerdam, 33 F.3d at 1361, 31 USPQ2d at 1760 (claim to a data structure *per se* held nonstatutory). Computer programs are viewed as computer listings, *per se*, i.e., the description or expression of the programs, are not physical things. They are neither computer components nor statutory processes, as they are not "acts" being performed. Such claimed computer programs do not define any structural and functional interrelationships between the computer program and the other claimed elements of a computer that permit that computer program's functionality to be realized.

This rejection could be overcome by amending the claims to recite that a result of the method is "displayed" or "outputted" (e.g. output to a user, a display, a memory, or another computer, etc.), or by amending the claims to include a step of a physical transformation of matter (e.g. assay), if such is supported in the specification as originally filed. For an updated discussion of statutory considerations with regard to non-functional descriptive material and computer-related inventions, see the Guidelines for Patent Eligible Subject Matter in the MPEP 2106, Section IV.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action and further elaborated on below to include the newly recited claim 47.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to start a microscope objective, measure pre-set criteria in terms of size, morphology, and characteristic cell markers and identify a rare cell. For the reasons set forth below, this constitutes undue experimentation.

b) and c) The specification provides examples for detecting **fetal** cells from blood smears of maternal blood. The method comprises the following steps, as described on page 10:

Two signals are defined, referred to hereinafter as the first signal and the second signal. As used herein, "signal" should be taken in its broadest sense, as a physical manifestation which

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can be detected and identified, thus carrying information. One simple and useful signal is the light emitted by a **fluorescent dye** selectively bound to a structure of interest. That signal indicates the presence of the structure, which might be difficult to detect absent the fluorescent dye.

Screening 103 is based on the first signal. The first signal, which in this exemplary embodiment indicates cell identity, may be generated by a fluorescent dye bound to an antibody against the hemoglobin t-chain, i.e., embryonal hemoglobin, for example. Alternatively, for example, a metric of each cell's similarity to the characteristic morphology of nucleated erythrocytes, discerned using cell recognition algorithms may serve as the first signal. In yet another example, the **first signal may be a measure of the presence of the characteristic color of fetal hemoglobin after staining with eosin and acid hematoxylin**. It should now be evident that any detectable indicator of the presence of fetal cells may serve as the first signal, subject to certain constraints noted below.

Diagnosing 105 is based on the second signal. The second signal, which in this exemplary embodiment indicates the presence of a particular genetic characteristic being tested for, may be generated, for example, by in situ PCR-amplification or PCR in situ hybridization or FISH. Cells that emit both signals, i.e., the cell is a fetal cell and contains the genetic characteristic being tested for, will be scored. Counts may be maintained of the number and strengths of the first and second signals detected.

Further, the specification teaches that cells are stained using various procedures, as outlined on pages 18 to 19. From this, samples are processed according to the methods of pages 23 to 27, in which the color image is processed from RGB to HLS signals.

The instant claims, however, **do not reflect such steps** of cell staining or cell tagging such that one of skill in the art would know how to perform the method of isolating a cell sample, fix a cell sample and locate **rare cell** candidates to produce a color image. Without steps of labeling or staining, the generation of a color signal for processing is not possible and the claims are not enabled. It is noted that the instant claims are drawn to rare cells and not to fetal cells, as Applicant argues in the response.

Further, it is unclear how the identification step occurs to locate a reagent dispensing system. The claimed step does not actually provide for applying a tag or label to any rare cell. It

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merely recites a system programmed to do so and it is unclear as to HOW this step occurs and what relationship it has to the other claimed method steps.

For the reasons set forth above, the claims are not enabled.

d) The invention is drawn to methods of rare cell image identification. However, the claims are not enabled, as there are no cellular identification labels or stains such that one of skill in the art would be able to generate an image for processing and identification of a rare cell.

e) It would have been well known in the art that increasing the sensitivity of microscopically detecting cellular characteristics requires staining or labeling. This is a more effective way than simply evaluating morphology alone. For example, Mesker et al. (Cytometry (1994) Vol. 17, pages 209-215; PTO Form 1449 document) teaches the detection of rare cell events using image cytometry in which markers are used to stain cells of interest in different colors. Analysis of the cell images, obtained at different wavelengths, result in high contrast to specifically recognize the different markers. Therefore, in order to generate a color image, staining and markers must be used. The instant claims, however, are not enabled for the generation of a color image.

f) and g) The skill of those in the art of cytometry is high. However, absent steps of labeling or staining in the claims, one of skill in the art would not know how to generate or receive a color image signal.

h) The claims are broad because they are drawn to receiving a color image without the appropriate steps in which to generate the image from the cell sample. The skilled practitioner would first turn to the instant specification for guidance to practice such methods. However, the instant specification indicates that labeling, marking, staining are necessary in order to generate

such an image. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows the same. Finally, said practitioner would turn to trial and error experimentation to determine if the claimed method steps would yield a color image. Such represents undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 recites, “starting a microscope objective from an origin...to locate and digitize”. It is unclear how the step of starting a microscope includes locating and digitizing a native or stained color image”. It appears as if a step is missing. Clarification is requested.

Claim 47 recites, “measuring pre-set criteria of the digitized image...in terms of size, morphology, and characteristic cell markers”. Does Applicant intend that the pre-set criteria are size, morphology, and characteristic cell markers? This is unclear and clarification through clearer claim language is requested.

Claim 47 recites, “measuring...while enhancing detection of”. It is unclear if these steps occur simultaneously, one after the other or in some other sequence. Clarification is requested.

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Claim 47 recites, "identifying said detected rare cell by using". There is insufficient antecedent basis in the claim for "detected rare cell". Perhaps Applicant intends "said detected rare cell candidate" or "said detected rare cell image". Clarification is requested.

Claim 47 recites, "identifying said detected rare cell by using the automatically recorded coordinates of said rare cell to locate over said rare cell a computer-controlled reagent dispensing system programmed to apply selectively a specific tag or label to said rare cell in situ. It is unclear what I intended by this step. It is unclear how identifying can locate a reagent dispensing system. See above enablement rejection. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,169,816 B1 (Ravkin). It is noted that this rejection is being re-applied, as a result of the amendments to the claims in which certain limitations have been deleted from the claim language.

The instant claims are drawn to a computer-controlled method for automated rare cell image identification. In regard to claims 16, 18, 40, 45, and 47, Ravkin teaches computer

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implemented imaging a smear of fetal nucleated red blood cells (NRBCs) and other objects, such as red blood cells (RBCs) and white blood cells (WBCs). The objects in the sample are stained with a fluorescent dye that selectively stains nuclei and a dye that selectively stains fetal hemoglobin in the cytoplasm of fetal NRBCs. These include two different illumination schemes, such that candidate regions of interest (blobs) are identified for further processing (column 1, lines 65-67 to column 2, lines 1-20). The invention is directed to an evaluation that includes enrichment of fetal NRBCs from maternal blood, positive identification of fetal NRBCs (signal one), and genetic analysis (signal two) (column 3, lines 30-33).

In regard to claims 47, step iii, Ravkin teaches that a set of features that identify fetal NRBCs are created to distinguish them from other types of cells. This is done by creating contrast in cells containing fetal hemoglobin and another type of contrast in cells having a nucleus. The slide is reacted with a reagent (antibody) to produce a signal (column 3, line 58-667 to column 4, lines 1-6). The images are processed to provide derivative images that are correlated to a region of interest. From there further analysis of only the region of interest is performed, such that the image falls into a specific class of object (column 7, lines 44-57). Ravkin teaches that the invention is carried out to identify objects for further analysis such as FISH. A FISH sample is prepared using probe that binds to a particular DNA sequence in the chromosomes in the sample and the probe is labeled. The preparation of the slides with reagent is automated (column 3, lines 1-10 and lines 27-57). Since step ii of claim 47 is so unclear the claim limitation has been interpreted broadly for the purposes of applying the prior art herein.

Ravkin teaches varying concentrations of rare cells as in claim 41 at column 3, lines 41-45.

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Conclusion

No claims are allowed.

The outstanding rejections under 35 USC 112, 1st paragraph for new matter have been withdrawn in view of the amendments to the claims.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

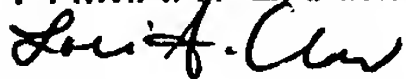
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

LORI A. CLOW, PH.D.
PRIMARY EXAMINER



September 3, 2007
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